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(54) SOLUBILIZING AGENT AND EXTERNAL PREPARATION CONTAINING THE SAME

(57) A solubilizing agent for an active ingredient which comprises 3-*l*-menthoxypropane-1,2-diol and an external preparation containing said solubilizing agent and an active ingredient.

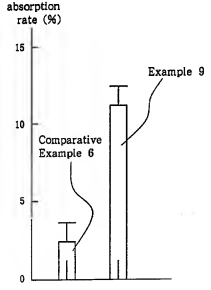

Fig. 1

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Description

Technical Field

The present invention relates to a solubilizing agent or solubilizer for a pharmaceutically effective ingredient and an external preparation containing the solubilizer. In particular, the present invention relates to a solubilizer for an efficacious ingredient used in a percutaneously absorbable preparation such as poultice or for a fat-soluble powder used in a pack, the solubilizer being excellent in solubilization of such an effective ingredient as well as in safety, stability, compatibility, inodorousness and refreshing, effect, and also relates to an external preparation containing the solubilizer.

Background Art

Up to this time, many attempts have been made to attain desirable curative effects by the percutaneous absorption of drugs. It is a significant problem to such percutaneously absorbable preparations how efficiently the drug (active ingredient as a drug) is released from the base, i.e., how efficiently the drug migrates from the base to the skin. In general, when attempting to design a preparation using some drug therein, there frequently occurs such a case that the drug crystallizes in the base because of its insufficient dissolution therein, resulting in poor drug release thereby to fail in giving a sufficient curative effect. Accordingly, the selection of an optimum solubilizer for a drug is an important factor for designing such a preparation. If an unsuitable solubilizer is selected for a drug, the release of the drug from the base is lowered due to the insufficient dissolution of the drug in the base, which leads to poor migration of the drug to an affected part thereby resulting in poor curative effect.

Solubilizers currently used for drugs include alcohols, glycols, several surfactants, essential oils such as mentha oil, crotamiton, methyl salicylate, glycol salicylate and fatty acid esters such as isopropyl myristate.

For example, Japanese Pat. Appln. Laid-Open Gazette No. 154413/1981 discloses an anti-inflammatory agent for external use which comprises both an oil-in-water emulsion containing a solution of flurbiprofen in a terpene or in a fatty acid ester and an aqueous base, and Japanese Pat. Appln. Laid-Open Gazette No. 98209/1982 discloses another anti-inflammatory agent for external use which is prepared by dissolving indomethacin in a mono- or poly-hydric alcohol or the like.

However, these solubilizers have problems that they have poor solbilizability (capability of solubilization) to cause the crystallization of a drug, that they are limited in use due to their odors, that they bleed from the base with the lapse of time due to their poor compatibility with the base, that they are poor in stability to cause therein decomposition or discoloration with the lapse of time and that they cause undesirable side effects due to their stimuli to the skin, resulting unsatisfactory effects in many cases.

Meanwhile, attempts have been made to get a powder which is soluble in fat or difficultly soluble in water (hereinafter referred to as "fat-soluble powder") to be contained in a pack for its practical use. However, a pack generally comprises a water-soluble base which exhibits extremely poor solubilizability for a fat-soluble powder, so that many of the above attempts were accompanied by the problems that the solubilization of the powder in the base was difficult and/or that the resulting pack was poor in stability to cause crystallization of the powder with the lapse of time even when the powder could be solubilized in the base in the preparation stage.

Disclosure of the Invention

The present invention aims at solving the above problems to provide a solubilizer which exhibits excellent solubilizability for a pharmaceutically effective ingredient and is excellent in safety, stability and compatibility, and provide an external preparation containing the solubilizer.

The above aim of the present invention can be attained by using 3-*ℓ*-menthoxypropane-1,2-diol as the solubilizer for a pharmaceutically effective ingredient.

Namely, the present invention resides in a solubilizer for a pharmaceutically effective ingredient which is composed of 3-*ℓ*-menthoxypropane-1,2-diol, and in an external preparation containing the solubilizer and a pharmaceutically effective ingredient.

The term "pharmaceutically effective ingredient" used in this specification refers to a drug used in a percutaneously absorbable preparation or a fat-soluble powder used in a pack.

3-*ℓ*-menthoxypropane-1,2-diol which is the solubilizer of the present invention, is a known substance described in, e.g., Japanese Pat. Appln. Laid-Open Gazette No. 88334/1983 as a substance having a cooling or refreshing activity. Further, Japanese Pat. Appln. Laid-Open Gazette No. 25908/1985 discloses that this compound is useful as a cosmetic material, has an excellent cooling effect and is extremely safe for the skin. However, there has not been made even any attempt to solubilize a pharmaceutically effective ingredient such as a drug by using said known substance, to say nothing of an attempt to get a drug solubilized by use of this substance to be absorbed percutaneously. In other words, such an

attempt has been made for the first time by the inventors of the present invention and the present invention is based on this entirely new finding.

According to the present invention, the amount of 3-*ℓ*-menthoxypropane-1,2-diol contained in an external preparation is 0.001 to 20% by weight of the total amount of the external preparation.

In particular, when the external preparation is a percutaneously absorbable preparation containing a drug as the effective ingredient and 3-*ℓ*-menthoxypropane-1,2-diol is used as a solubilizer, the amount of 3-*ℓ*-menthoxypropane-1,2-diol used will be 0.1 to 20% by weight, preferably 0.5 to 10% by weight, of the total amount of the external preparation. When the amount is less than 0.1% by weight, no sufficient effects as the solubilizer will be exhibited, while when it exceeds 20% by weight, no stable preparation will be prepared.

The drug to be used in the percutaneously absorbable preparation which is one of the external preparations according to the present invention is not particularly limited but may be any one selected from among known conventional drugs. Such drugs include steroidal anti-inflammatory agents such as prednisolone, dexamethasone, hydrocortisone, fluocinolone acetonide, betamethasone valerate, betamethasone dipropionate, clobetasone butyrate and prednisolone succinate; nonsteroidal anti-inflammatory agents such as indomethacin, diclofenac, ibuprofen, ketoprofen, flufenamic acid, ketorolac, flurbiprofen, felbinac, suprofen, pranoprofen, tiaprofen, loxoprofen and tenidap, and their ester derivatives; antiallergic agents such as tranilast, azelastine, ketotifen, ibudilast and emedastine; antihistamic agents such as diphenhydramine, chlorpheniramine, promethazine and tripelennamine; central nervous system stimulants such as chlorpromazine, nitrazepam, diazepam, phenobarbital and reserpine; hormones such as insulin, testosterone, norethisterone, methyltestosterone, progesterone and estradiol; antihypertensive agents such as clonidine, reserpine and guanethidine sulfate; cardiotonics such as digitoxin and digoxin; antiarrhythmic agents such as propranolol hydrochloride, procainamide hydrochloride, ajimalin, pindolol and tulobuterol hydrochloride; coronary vasodilators such as nitroglycerin, isosorbide dinitrate, papaverine hydrochloride and nifedipine; local anesthetics such as lidocaine, benzocaine, procaine hydrochloride and tetracaine; analgetic agents such as morphine, aspirin, codeine, acetanilide and aminopyrine; skeletal muscle relaxants such as eperisone, tizanidine, tolperisone and inaperisone; antifungal agents such as acetophenylamine, nitrofurazone, pentamycin, naphthiomate, miconazole, omoconazole, clotrimazole, butenafine hydrochloride and bifonazole; antineoplastic agents such as 5-fluorouracil, busulfan, actinomycin, bleomycin and mitomycin; antidysurics such as terodiline hydrochloride and oxybutynin hydrochloride; antiepileptics such as nitrazepam and meprobamate; antiparkinson agents such as chlorzoxazone and levodopa; assistant to the prohibition of smoking such as nicotine; vitamins and prostaglandins, though the drug usable in the percutaneously absorbable preparation is of course not limited to them.

The amount of the drug used is preferably 0.001 to 20% by weight, more preferably 0.5 to 10% by weight, of the total amount of the external preparation, though it is not particularly limited.

The dosage form of the percutaneously absorbable preparation of the present invention is not particularly limited, but may be any one selected from among conventional poultice, plaster, ointment, gel, cream, gel-type cream, lotion, reserver-type patch, liniment, aerosol and so forth.

The poultice and plaster according to the present invention will now be described below.

In preparing the poultice, a hydrophilic base comprising a water-soluble polymer, a polyhydric alcohol and water is used in consideration of long-term stability, releasability, percutaneous absorbability and safety for the skin.

The water-soluble polymer to be used in the hydrophilic base may be one or more members suitably selected from the group consisting of gelatin, casein, pullulan, dextran, sodium alginate, soluble starch, carboxystarch, dextrin, carboxymethylcellulose, sodium carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, polyethylene oxide, polyacrylic acid, polyacrylamide, polysodium acrylate, polyvinylpyrrolidone, carboxyvinyl polymer, polyvinyl ether, methoxyethylene-maleic anhydride copolymer, isobutylenemaleic anhydride copolymer, N-vinylacetamide, copolymer comprising N-vinylacetamide and acrylic acid and/or acrylate salt and so forth. The amount of the water-soluble polymer used is 1 to 30% by weight, preferably 1 to 20% by weight, more preferably 1 to 15% by weight, based on the total amount of the preparation. When the amount is less than 1% by weight, the resulting preparation will have too low a viscosity to retain its shape, while when it exceeds 30% by weight, the resulting mixture of the constituents will have a high viscosity to lower the workability in preparing a homogeneous dispersion of the constituents or in applying the dispersion.

The polyhydric alcohol is one or more members suitably selected from the group consisting of polyethylene glycol, propylene glycol, dipropylene glycol, polypropylene glycol, 1,3-butylene glycol, 1,4-butylene glycol, isobutylene glycol, glycerol, diglycerol, sorbitol and so forth. The amount of the polyhydric alcohol used is 10 to 90% by weight, preferably 10 to 70% by weight, more preferably 20 to 60% by weight. When the amount is less than 10% by weight, the resulting preparation will exhibit poor humectant effect, while when it exceeds 90% by weight, the solubility of the water-soluble polymer will be adversely affected. The amount of water used is 10 to 90% by weight, preferably 20 to 80% by weight. The water serves to solubilize the water-soluble polymer to thereby make the polymer develop its thickening, cohesive and shape-retaining properties.

If necessary, the base of the poultice may further contain one or more crosslinking agents in addition to the above essential components. The crosslking agents include polyvalent metal compounds such as aluminum hydroxide, alu-

minum chloride, calcium hydroxide, calcium chloride, aluminum sulfate, aluminum ammonium sulfate, aluminum potassium sulfate, magnesium aluminometasilicate and dihydroxyaluminum aminoacetate; and compounds each having at least two epoxy groups in the molecule such as ethylene glycol diglycidyl ether, polyethylene glycol diglycidyl ether, propylene glycol diglycidyl ether, polypropylene glycol diglycidyl ether, polytetramethylene glycol diglycidyl ether, glycerol polyglycidyl ether, polyglycerol polyglycidyl ether, sorbitol polyglycidyl ether, sorbitan polyglycidyl ether, trimethylolpropane polyglycidyl ether, pentaerythritol polyglycidyl ether, resorcinol diglycidyl ether, neopentyl glycol diglycidyl ether and 1,6-hexanediol diglycidyl ether.

Further, the base of the poultice may contain one or more additives suitably selected from among fillers such as kaolin, zinc oxide, titanium dioxide, talc, bentonite and synthetic aluminum silicate; antiseptics such as thymol, methyl paraben and ethyl paraben; antioxidants such as ascorbic acid, stearic esters, dibutylhydroxytoluene, butylhydroxyanisole, gallic esters, vitamin E, vitamin E acetate and disodium edetate; ultraviolet absorbers such as 2-hydroxy-4-methoxybenzophenone, ethyl p-aminobenzoate, 2-(2-hydroxy-5-methylphenyl)benzotriazole, glycol salicylate, methyl salicylate and phenyl salicyalte; and emulsifying agents such as fatty acid esters of sorbitan, fatty acid esters of glycerol, fatty acid esters of decaglycerol, fatty acid esters of polyoxyethylene sorbitan, fatty acid esters of polyethylene glycol and polyoxyethylene alkyl ethers.

It is essential that the support of the poultice is made of a material which has no influence on the release of a drug, i.e., that the support neither interacts with a drug nor adsorb a drug. The support is selected from the group consisting of films and sheets of polyethylene, polypropylene, polyvinyl chloride, polyester, nylon and polyurethane; porous materials, expanded materials and woven and nonwoven fabrics of these polymers; laminates each comprising one or more members selected from the group consisting of these films and sheets and one or more members selected from the group consisting of these materials and fabrics and so forth. The release sheet of the poultice according to the present invention may be selected from the group consisting of films of polyethylene, polypropylene and polyester; products of release treatment of these films with silicone compounds; release paper and so forth.

The preparation of the poultice will now be described, though the poultice can be easily prepared by known processes.

For example, a nonsteroidal anti-inflammatory agent selected from the group consisting of diclofenac, ketoprofen, flurbiprofen, tenidap, loxoprofen, ketorolac, felbinac, suprofen, indomethacin and ester derivatives and salts of these drugs is solubilized in 3-*ℓ*-menthoxypropane-1,2-diol to form a solution (A) which may, if necessary, be incorporated with one or more additives selected from the group consisting of a stabilizer, an antioxidant, an ultraviolet absorber, an emulsifying agent, an antiseptic, an antimicrobial and so forth. Separately, a water-soluble polymer is mixed into, dispersed and solubilized in a polyhydric alcohol or water to form a homogeneous paste (B). The solution (A) is added to the paste (B) to form a homogeneous dispersion. This dispersion is spread directly on a support, or alternatively it is once spread on a paper or film treated with a releasant and thereafter transferred to a support by pressing. Thus, a poultice according to the present invention is prepared. The above-mentioned procedure for mixing base materials, a drug and other components is just one example, not limiting the procedure for preparing the poultice according to the present invention.

The plaster according to the present invention comprises, for example, (a) a nonsteroidal anti-inflammatory agent selected from the group consisting of diclofenac, ketoprofen, flurbiprofen, tenidap, loxoprofen, ketorolac, felbinac, suprofen and ester derivatives and salts of these drugs, (b) a solubilizer comprising a rosin ester derivative and 3-*ℓ*-menthoxypropane-1,2-diol, (c) a styrene-isoprene-styrene block copolymer or an acrylic adhesive as the base polymer and (d) a softening agent or a known plaster base.

The support for the plaster is selected from among polypropyene fabrics and polyester fabrics which have no influence on the release of a nonsteroidal anti-inflammatory agent. The polyester fabric to be used as the support is preferably one made of polyethylene terephthalate (PET) or polybutylene terephthalate (PBT). In order to attain excellent release of a nonsteroidal anti-inflammatory agent, it is essential that the support neither interacts with a nonsteroidal anti-inflammatory agent nor adsorb it. From this standpoint, the optimum polymer constituting the support is polypropylene, PET or PBT. The use of a support made of polypropylene, PET or PBT prevents the adsorption of a drug to the support to enable excellent release of the drug.

The plaster according to the present invention is provided with such stretchability that the average stresses at 50% elongation in lengthwise and widthwise directions each is 0.3 kg/cm or below, so that it can be applied to a bend of human skin. By virtue of this stretchability, the plaster according to the present invention not only is enabled to be used expediently and to follow the move of the skin thereby to decrease the friction and pressure during the use of the plaster on the skin, thus causing little side effects (such as contact dermatitis).

The plaster according to the present invention is characterized by using a mixture comprising a rosin ester derivative, which is well known by those skilled in the art as a tackifier resin, and 3-*ℓ*-menthoxypropane-1,2-diol at a specific ratio thereby to attain excellent solubility of a drug surprisingly. Further, the use of this mixture improves the release of a drug remarkably. In order to attain more excellent solubility of a drug such as nonsteroidal anti-inflammatory agent in the base and more excellent release thereof from the base, it is preferable that a nonsteroidal anti-inflammatory agent, a rosin ester derivative and 3-*ℓ*-menthoxypropane-1,2-diol be contained at a weight ratio of 1 : (2 to 25) : (1 to 10). When these components are contained at such a ratio as above, the drug exhibits high solubility and releasability.

The term "rosin ester derivative" used in this specification refers to any of the products prepared by esterifying various rosins and subjecting the obtained esters to hydrogenation or purification. The esters include methyl ester, glycerol ester and pentaerythritol ester. The rosin ester derivatives include Ester Gum A, AA-G, H and HP (trade names, products of Arakawa Chemical Industry Co, LTD.), Hariester-L, S and P (trade names, products of Harima Chemicals, Inc.), Super Ester A-75 (trade name, a product of Arakawa Chemical Industry Co., Ltd.), KE-311 (trade name, a product of Arakawa Chemical Industry Co., Ltd.), Hercolyn D (trade name, a product of Hercules Inc.) and Foral 85 and 105 (trade names, products of Hercules Inc.).

The base polymer of the plaster may be selected from conventional ones in consideration of safety for the skin, releasability of a drug and adhesion to the skin. From the standpoint of the release characteristics of a nonsteroidal anti-inflammatory agent, it is preferable that the base polymer be a styrene-isoprene-styrene block copolymer having a particularly low polarity. Such block copolymers include Cariflex TR-1107, TR-1111, TR-1112 and TR-1117 (trade names, products of Shell Chemical) and Solprene 428 (trade name, a product of Phillips Petroleum). These styrene-isoprene-styrene block copolymers may be each used together with other polymer such as polyisobutylene. Vistanex (trade name, a product of Exxon Kagaku) is preferably used as the polyisobutylene.

The softening agent serves to plasticize or soften the styrene-isoprene-styrene block copolymer used as the base polymer to thereby keep the adhesion of the plaster to the skin at a proper level. The softening agent may be selected from the group consisting of almond oil, olive oil, camellia oil, persic oil, peanut oil, liquid paraffin and so forth. The amount of the softening agent used is preferably 150 to 350 parts by weight per 100 parts by weight of the styrene-isoprene-styrene block copolymer.

The content of a drug is preferably 70 to 1200 μg/cm^2 from the standpoints of therapeutically effective release of a drug and availability thereof, though it is not particularly limited. Preferable proportions of a drug, rosin ester derivative, 3-ℓ-menthoxypropane-1,2-diol, styrene-isoprene-styrene block copolymer and softening agent are as follows.

That is, the plaster comprises 0.5 to 10% by weight of a drug, 5 to 70% by weight of a rosin ester derivative, 0.5 to 10% by weight of 3-ℓ-menthoxypropane-1,2-diol, 5 to 40% by weight of a styrene-isoprene-styrene block copolymer and 10 to 75% by weight of a softening agent, each percentage being based on the total amount.

The plaster according to the present invention can be easily prepared by known processes. For example, it can be prepared by mixing a styrene-isoprene-styrene block copolymer with a softening agent and a rosin ester derivative under heating at 120 to 160°C by the use of a mixing machine such as kneader or mixer, adding a drug and 3-ℓ-menthoxypropane-1,2-diol to the obtained mixture, and applying the resulting mixture to a support either by spreading the mixture directly on a woven or nonwoven fabric of polypropylene or polyester or by spreading the mixture on a paper or film treated with a releasant and thereafter transferring the spread mixture to a desired support by pressing.

Now, brief description will be made on other percutaneously absorbable preparations (such as ointment, gel, cream, gel-type cream, lotion, reserver-type patch, liniment and aerosol) according to the present invention.

The ointment according to the present invention comprises at least higher fatty acid (such as myristic acid) or an ester thereof, a wax (such as spermaceti), a surfactant (such as polyoxyethylene) and a hydrocarbon (such as hydrophilic vaseline) in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol.

The ointment can be prepared by, for example, mixing 5 to 15% by weight of a higher fatty acid or an ester thereof with 1 to 10% by weight of a surfactant, 0.5 to 10% by weight of a drug and 0.5 to 10% by weight of 3-ℓ-menthoxypropane-1,2-diol either at room temperature or under heating, adding 4 to 10% by weight of a wax and 50 to 90% by weight of a hydrocarbon to the obtained mixture, heating or heat-melting the resulting mixture, keeping the mixture at 50 to 100°C to make the whole of the mixture a transparent solution, homogenating the solution with a homomixer, and lowering the temperature of the resulting solution to room temperature under stirring.

The gel according to the present invention comprises at least a lower alcohol (such as ethanol), water, a gelling agent (such as carboxyvinyl polymer) and a neutralizing agent (such as triethanolamine) in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol.

The gel can be prepared, for example, as follows: 0.5 to 5% by weight of a gelling agent is swollen with at most 55% by weight of water; separately, 0.5 to 10% by weight of a drug is solubilized in 0.5 to 10% by weight of 3-ℓ-menthoxypropane-1,2-diol and the obtained solution is further solubilized in a mixture comprising at most 40% by weight of a glycol and at most 60% by weight of a lower alcohol; the obtained solution is mixed with the gelling agent swollen above; and the resulting mixture is adjusted to pH4-7 by the addition of a neutralizing agent, thus giving a gel according to the present invention.

The cream according to the present invention comprises at least a higher fatty acid ester (such as myristate), water, a hydrocarbon (such as liquid paraffin) and an emulsifying agent (such as polyoxyethylene alkyl ether) in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol.

The cream can be prepared by stirring a mixture comprising a drug, 3-ℓ-menthoxypropane-1,2-diol, a higher fatty acid ester, water, a hydrocarbon and an emulsifying agent in proper amounts.

A gel-type cream has intermediate properties between a gel and a cream and can be prepared by adding a gelling agent such as a carboxyvinyl polymer to components of cream as described above and adjusting the resulting mixture to pH4-8, preferably pH5-6.5 by the addition of a neutralizing agent such as diisopropanolamine.

The gel-type cream according to the present invention can be prepared, for example, as follows: 0.5 to 10% by weight of a drug is solubilized in 0.5 to 10% by weight of 3-ℓ-menthoxypropane-1,2-diol and the obtained solution is further solubilized in a mixture comprising at most 25% by weight of a higher fatty acid ester and at most 40% by weight of a lower alcohol, followed by the addition of at most 5% by weight of an emulsifying agent; separately, 0.5 to 5% by weight of a gelling agent is swollen with water; the swollen agent is mixed with the solution prepared above; and the obtained mixture is homogenized with a homomixer and adjusted to pH4-8 by the addition of a neutralizing agent.

The lotion according to the present invention comprises at least a lower alcohol (such as ethanol) and water and/or a glycol in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol.

The lotion can be prepared by stirring a mixture comprising a drug, 3-ℓ-menthoxypropane-1,2-diol, a lower alcohol and water and/or a glycol in proper amounts.

The reserver-type patch according to the present invention comprises at least (1) a backing layer, (2) a drug reserving layer, (3) a drug releasing layer and (4) a pressure-sensitive adhesive layer, wherein the base of the drug reserving layer (2) comprises one mixture selected from the group consisting of

(a) mixture comprising at least a glycol, a lower alcohol, water and a water-soluble polymer,
(b) a mixture comprising at least an aliphatic alcohol and a polyhydric alcohol
and
(c) a mixture comprising at least a paraffin and a silicon compound,
in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol.

The liniment according to the present invention comprises at least an alcohol (such as ethanol or polyethylene glycol), water and an ester of fatty acid (such as adipic acid or sebacic acid) in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol.

The liniment can be prepared by dissolving 0.5 to 10% by weight of a drug in 0.5 to 10% by weight of 3-ℓ-menthoxypropane-1,2-diol and mixing the obtained solution with 10 to 70% by weight of an alcohol, at most 55% by weight of water and at most 60% by weight of a fatty acid ester under stirring.

The aerosol according to the present invention comprises at least a lower alcohol, water and dimethyl ether and/or liquefied petroleum gas in addition to a drug and 3-ℓ-menthoxypropane-1,2-diol, and may further contain an auxiliary drug such as camphor α-tocopherol or menthol at need.

The aerosol can be prepared by dissolving 0.5 to 10% by weight of a drug in 0.5 to 10% by weight of 3-ℓ-menthoxypropane-1,2-diol, adding a lower alcohol and water to the obtained solution, charging the obtained mixture into an aerosol container and injecting dimethyl ether and/or liquefied petroleum gas as a propellant into the container.

The percutaneously absorbable preparations according to the present invention may further contain various pharmacologically acceptable additives, so far as the object of the present invention is not marred. Examples of such additives include a stabilizer, an antioxidant, a perfume, a filler, an ultraviolet absorber, an antihistamine, an antiseptic, an antimicrobial agent and an absorbefacient.

Then, the pack according to the present invention will be described. The pack according to the present invention is characterized by using 3-ℓ-menthoxypropane-1,2-diol as the solubilizer for a fat-soluble powder used as the pharmaceutically effective ingredient.

The term "fat-soluble powder" used in this specification refers to a powder which is insoluble or difficultly soluble in water, and such a powder includes pharmaceutically effective ingredients and various additives used in the preparation of pack. In particular, it is preferable that the powder be selected from the group consisting of glycyrrhetinic acid, stearyl glycyrrhetinate, glycyrrhizinic acid, L-ascorbyl stearate, L-ascorbyl palmitate, calciferol, cholecalciferol, pionin and isopropylmethylphenol. The use of 3-ℓ-menthoxypropane-1,2-diol as the solubilizer for a fat-soluble powder as described above enables the stable dissolution of the powder in the base to give an odorless pack imparting comfortable refreshing refrigeration to the skin.

It is preferable that the content of 3-ℓ-menthoxypropane-1,2-diol in the pack be in the range of 0.001 to 5% by weight. When the content is less than 0.001% by weight, no satisfactory solubilizability will be attained, while when it exceeds 5% by weight, the resulting pack will be poor in physical properties and feelings in use.

The dosage form of the pack according to the present invention is not particularly limited, but may be any conventional one selected from the group consisting of face cleasing packs (of creamy, clayey and foam types), sheet packs (of pressure-sensitive adhesive type and impregnation type), peel-off pack (of film forming type) and so forth. Of course, the pack may further contain a conventional filler, perfume or the like at need.

Brief Description of Drawing

Fig. 1 is a graph showing the human absorption rates of the plasters of Example 9 and Comparative Example 6.

DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention will be better understood by Examples which should not be construed as limiting the invention, in comparison with Comparative Examples.

Example 1 poultice

(A)	3-ℓ-menthoxypropane-1,2-diol	1.0% by weight
	diclofenac	0.5% by weight
(B)	purified water	48.5% by weight
	gelatin	8.0% by weight
	kaoin	1.0% by weight
	glycerol	35.0% by weight
	polysodium acrylate	2.0% by weight
	polyvinyl alcohol	3.0% by weight
	aluminum hydroxide	1.0% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polypropylene nonwoven fabric with a speader to obtain a percutaneously absorbable preparation layer having a thickness of 1 mm. Then, the preparation layer was covered with a polypropylene film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Example 2 poultice

(A)	3-ℓ-menthoxypropane-1,2-diol	2.0% by weight
	loxoprofen	1.0% by weight
	thymol	0.1% by weight
(B)	purified water	62.4% by weight
	gelatin	3.0% by weight
	titanium oxide	1.0% by weight
	glycerol	25.0% by weight
	polysodium acrylate	3.0% by weight
	carboxymethyl cellulose	1.0% by weight
	ethylene glycol diglycidyl ether	1.0% by weight
	sorbitan fatty acid ester	0.5% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polyester nonwoven fabric with a spreader to obtain a percutaneously absorbable preparation layer having a thickness of 0.5 mm. Then, the preparation layer was covered with a polyethylene film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Example 3 poultice

(A)	3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
	ibuprofen	0.5% by weight
	ethyl paraben	0.2% by weight
(B)	purified water	42.3% by weight
	methoxyethylene anhydrous maleic acid copolymer	5.0% by weight
	synthetic aluminium silicate	3.0% by weight
	glycerol	40.0% by weight
	polyacrylic acid	2.0% by weight
	polyvinyl alcohol	2.5% by weight
	calcium hydroxide	1.5% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polyurethane film with a spreader to obtain a percutaneously absorbable preparation layer having a thickness of 1 mm. Then, the preparation layer was covered with a polyurethane film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Example 4 poultice

(A)	3-ℓ-menthoxypropane-1,2-diol	2.0% by weight
	ketoprofen	0.5% by weight
(B)	purified water	36.0% by weight
	N-vinylacetamide	5.0% by weight
	glycerol	50.0% by weight
	polyacrylic acid	3.0% by weight
	carboxymethyl cellulose	1.0% by weight
	magnesium metasilicate alminate	1.5% by weight
	fatty acid esters of glycerol	1.0% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polyester nonwoven fabric with a spreader to obtain a percutaneously absorbable preparation layer having a thickness of 1 mm. Then, the preparation layer was covered with a polyester film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Comparative Example 1 poultice

(A)	crotamiton	1.0% by weight
	suprofen	0.8% by weight
(B)	purified water	54.2% by weight
	gelatin	6.0% by weight
	bentonite	5.0% by weight
	glycerol	25.0% by weight
	sodium alginate	2.0% by weight
	polyethylene oxide	4.0% by weight
	aluminum sulfate	1.5% by weight
	fatty acid esters of polyethylene glycol	0.5% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polyvinyl chloride with a spreader to obtain a percutaneously absorbable preparation layer having a thickness of 0.3 mm. Then, the preparation layer was covered with a polypropylene film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Comparative Example 2 poultice

(A)	glycerol salicylate	2.0% by weight
	ketoprofen	0.5% by weight
(B)	purified water	36.0% by weight
	N-vinylacetamide	5.0% by weight
	fatty acid esters of glycerol	1.0% by weight
	glycerol	50.0% by weight
	polyacrylic acid	3.0% by weight
	carboxymethyl cellulose	1.0% by weight
	magnesium metasilicate alminate	1.5% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polyester nonwoven fabric with a spreader to obtain a percutaneously absorbable preparation layer having a thickness of 1 mm. Then, the preparation layer was covered with a polyester film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Comparative Example 3 poultice

(A)	butylene glycol	4.0% by weight
	mentha	1.0% by weight
	loxoprofen	0.5% by weight
(B)	purified water	47.5% by weight
	gelatine	3.0% by weight
	kaolin	1.0% by weight
	glycerol	35.0% by weight
	polysodium acrylate	3.0% by weight
	carboxyvinyl polymer	2.5% by weight
	dextrin	2.0% by weight
	sorbitan polyglycidyl ether	0.5% by weight

The above ingredients were solubilized together and agitated thereby to obtain a homogeneous paste. The paste was applied on a polypropylene nonwoven fabric with a spreader to obtain a percutaneously absorbable preparation layer having a thickness of 1 mm. Then, the preparation layer was covered with a polyester film and cut into pieces each having a predetermined size thereby to obtain intended pharmaceutical products.

Example 5 plaster

styrene-isoprene-styrene block copolymer	22.5% by weight
polyisobutylene	5.0% by weight
tackifier (rosin ester)	15.0% by weight
liquid paraffin	56.0% by weight
3-*ℓ*-menthoxypropane-1,2-diol	1.0% by weight
ketotifen	0.5% by weight

The above components were agitated under heating, thereby obtaining a paste. The paste was spread on a foundation to obtain a tape containing ketotifen.

Example 6 plaster

pressure-sensitive adhesive of acrylic resin solubilizer type (trade name: NISSETSU PE-300)	77.0% by weight (in terms of solids)
3-ℓ-menthoxypropane-1,2-diol	15.0% by weight
isosorbide dinitrate	8.0% by weight

The above components were mixed together to obtain a paste. The paste was spread on a foundation and then freed of the solvent by evaporation thereby to obtain a tape containing isosorbide dinitrate.

Example 7 plaster

silicone adhesive (trade name: BIO-PSA X7-2920)	89.0% by weight (in terms of solids)
3-ℓ-menthoxypropane-1,2-diol	7.0% by weight
clonidine	4.0% by weight

The above components were agitated and mixed together to obtain a paste. The paste was spread on a foundation and then freed of the solvent by evaporation thereby to obtain a tape containing clonidine.

Comparative Example 4 plaster

silicone adhesive (trade name: BIO-PSA X7-2920)	96.0% by weight (in terms of solids)
clonidine	4.0% by weight

The above components were mixed together under agitation to obtain a paste. The paste was spread on a foundation and then freed from the solvent by evaporation thereby to obtain a tape containing clonidine. This Comparative Example indicates a formulation which was the same as Example 7 except for 4, 3-ℓ-menthoxypropane-1,2-diol.

Comparative Example 5 plaster

silicone adhesive	89.0% by weight
(trade name: BIO-PSA X7-2920)	(in terms of solids)
isopropyl myristate	7.0% by weight
clonidine	4.0% by weight

The above components were agitated and mixed together to obtain a paste. The paste was spread on a foundation and then freed of the solvent by evaporation thereby to obtain a tape containing clonidine. This Comparative Example 5 indicates a formulation which was the same as Example 7 except that isopropyl myristate was substituted for the 3-ℓ-menthoxypropane-1,2-diol used in Example 7.

Example 8 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	25.0% by weight
liquid paraffin	59.0% by weight
rosin ester derivative (trade name: Ester Gum AA-G)	5.0% by weight
3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
diclofenac	1.0% by weight

The components of the above prescription were mixed by a kneader to obtain a paste. Thereafter, the paste was applied directly on a PBT woven fabric and then covered with a liner to obtain a plaster.

Example 9 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	20.0% by weight
liquid paraffin	43.5% by weight
polyisobutylene (trade name: Vistanex)	10.0% by weight
rosin ester derivative (trade name: KE-311)	21.5% by weight
3-ℓ-menthoxypropane-1,2-diol	4.0% by weight
diclofenac	1.0% by weight

The components of the above prescription were mixed by a mixer to obtain a paste. The paste was applied on a plastic film previously endowed with releasability and then covered with a PET woven fabric and pressure-contact transferred to obtain a plaster.

Example 10 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	21.0% by weight
liquid paraffin	63.0% by weight
rosin ester derivative (trade name: KE-311)	10.0% by weight
3-ℓ-menthoxypropane-1,2-diol	4.0% by weight
diclofenac	2.0% by weight

The components of the above prescription were mixed together by a kneader to obtain a paste. The paste was applied on a plastic film previously endowed with releasability and, covered tereon with a PBT nonwoven fabric and pressure-contact transferred to obtain a plaster.

Example 11 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	30.0% by weight
liquid paraffin	57.0% by weight
rosin ester derivative (trade name: Ester Gum H)	7.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
diclofenac	1.0% by weight

The components of the above prescription were mixed together by a kneader to obtain a paste. The paste was applied on a plastic film previously endowed with releasability, thereon covered with a polypropylene nonwoven fabric and pressure-contact transferred to obtain a plaster.

Example 12 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	15.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	23.0% by weight
rosin ester derivative (trade name: Ester Gum H)	42.0% by weight
3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
diclofenac	5.0% by weight

The components of the above prescription were mixed together by a kneader to obtain a paste. The paste was applied on a plastic film previously endowed with releasability, thereon covered with a polypropylene nonwoven fabric and pressure-contact transferred to obtain a plaster.

Example 13 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1112)	18.0% by weight
liquid paraffin	54.5% by weight
rosin ester derivative (trade name: Foral 105)	18.5% by weight
3-ℓ-menthoxypropane-1,2-diol	6.0% by weight
diclofenac methyl ester	3.0% by weight

A plaster was obtained in the same manner as in Example 8.

Example 14 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	25.0% by weight
liquid paraffin	68.0% by weight
rosin ester derivative (trade name: Ester Gum AA-G)	5.0% by weight
3-ℓ-menthoxypropane-1,2-diol	1.5% by weight
ketoprofen	0.5% by weight

A plaster was obtained in the same manner as in Example 9.

Example 15 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	20.0% by weight
liquid paraffin	43.5% by weight
rosin ester derivative (trade name: KE-311)	30.5% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
ketoprofen	3.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 16 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	15.0% by weight
polyisobutene (trade name: Vistanex)	7.0% by weight
liquid paraffin	23.0% by weight
rosin ester derivative (trade name: Ester Gum H)	40.0% by weight
3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
ketoprofen	5.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 17 plaster

styrene-isoprene-styrene block copolymer (trade name: Solprene 418)	28.0% by weight
polybutene	5.0% by weight
liquid paraffin	57.7% by weight
rosin ester derivative (trade name: KE-311)	7.0% by weight
3-ℓ-menthoxypropane-1,2-diol	1.8% by weight
flurbiprofen	0.5% by weight

A plaster was obtained in the same manner as in Example 12.

Example 18 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	21.0% by weight
liquid paraffin	66.8% by weight
rosin ester derivative (trade name: KE-311)	7.2% by weight
3-ℓ-menthoxypropane-1,2-diol	4.0% by weight
flurbiprofen	1.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 19 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	21.0% by weight
liquid paraffin	45.0% by weight
rosin ester derivative (trade name: KE-311)	20.0% by weight
3-ℓ-menthoxypropane-1,2-diol	9.0% by weight
flurbiprofen	5.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 20 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	11.0% by weight
styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	11.0% by weight
liquid paraffin	44.0% by weight
rosin ester derivative (trade name: Ester Gum AA-G)	26.0% by weight
3-*l*-menthoxypropane-1,2-diol	7.0% by weight
flurbiprofen	1.0% by weight

A plaster was obtained in the same manner as in Example 12.

Example 21 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	30.0% by weight
liquid paraffin	56.0% by weight
rosin ester derivative (trade name: KE-311)	8.0% by weight
3-*l*-menthoxypropane-1,2-diol	5.0% by weight
loxoprofen	1.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 22 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	12.0% by weight
liquid paraffin	28.0% by weight
rosin ester derivative (trade name: Ester Gum H)	40.0% by weight
3-*l*-menthoxypropane-1,2-diol	12.0% by weight
loxoprofen	8.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 23 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1112)	21.0% by weight
liquid paraffin	50.0% by weight
rosin ester derivative (trade name: Ester Gum H)	20.5% by weight
3-ℓ-menthoxypropane-1,2-diol	5.5% by weight
loxoprofen	3.0% by weight

A plaster was obtained in the same manner as in Example 12.

Example 24 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	10.0% by weight
liquid paraffin	43.0% by weight
rosin ester derivative (trade name: KE-311)	35.0% by weight
3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
sodium loxoprofen	2.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 25 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	20.0% by weight
liquid paraffin	47.0% by weight
rosin ester derivative (trade name: Ester Gum H)	21.0% by weight
3-ℓ-menthoxypropane-1,2-diol	9.0% by weight
sodium loxoprofen	3.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 26 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	22.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	52.0% by weight
rosin ester derivative (trade name: Hercolyn D)	12.0% by weight
3-ℓ-menthoxypropane-1,2-diol	7.0% by weight
loxoprofen	2.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 27 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	20.0% by weight
liquid paraffin	38.0% by weight
rosin ester derivative (trade name: KE-311)	30.0% by weight
3-ℓ-menthoxypropane-1,2-diol	8.0% by weight
ketorolac	4.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 28 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	28.0% by weight
liquid paraffin	57.5% by weight
rosin ester derivative (trade name: Ester Gum H)	9.0% by weight
3-ℓ-menthoxypropane-1,2-diol	4.5% by weight
ketorolac	1.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 29 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1112)	21.0% by weight
liquid paraffin	53.0% by weight
rosin ester derivative (trade name: Ester Gum H)	10.0% by weight
3-ℓ-menthoxypropane-1,2-diol	14.0% by weight
ketorolac tromethamine	2.0% by weight

A plaster was obtained in the same manner as in Example 12.

Example 30 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	33.0% by weight
liquid paraffin	60.0% by weight
rosin ester derivative (trade name: Foral 105)	5.0% by weight
3-ℓ-menthoxypropane-1,2-diol	1.5% by weight
ketorolac	0.5% by weight

A plaster was obtained in the same manner as in Example 11.

Example 31 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	20.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	55.0% by weight
rosin ester derivative (trade name: KE-311)	10.0% by weight
3-ℓ-menthoxypropane-1,2-diol	8.0% by weight
ketoprofen	2.0% by weight

A plaster was obtained in the same manner as in Example 8.

Example 32 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	15.0% by weight
polyisobutylene (trade name: Vistanex)	14.0% by weight
liquid paraffin	38.0% by weight
rosin ester derivative (trade name: KE-311)	25.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
ketoprofen	3.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 33 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	22.0% by weight
polyisobutylene (trade name: Vistanex)	8.0% by weight
liquid paraffin	46.0% by weight
rosin ester derivative (trade name: KE-311)	14.0% by weight
3-ℓ-menthoxypropane-1,2-diol	8.0% by weight
ketorolac	2.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 34 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	15.0% by weight
polyisobutylene (trade name: Vistanex)	12.0% by weight
liquid paraffin	27.0% by weight
rosin ester derivative (trade name: KE-311)	38.0% by weight
3-ℓ-menthoxypropane-1,2-diol	4.0% by weight
ketorolac	4.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 35 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	20.0% by weight
liquid paraffin	45.5% by weight
rosin ester derivative (trade name: KE-311)	30.5% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
felbinac	1.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 36 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	15.0% by weight
polyisobutylene (trade name: Vistanex)	14.0% by weight
liquid paraffin	38.0% by weight
rosin ester derivative (trade name: KE-311)	26.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
felbinac	2.0% by weight

A plaster was obtained in the same manner as in Example 12.

Example 37 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	22.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	52.0% by weight
rosin ester derivative (trade name: Hercolyn D)	12.0% by weight
3-ℓ-menthoxypropane-1,2-diol	7.0% by weight
felbinac	2.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 38 plaster

styrene-isoprene-styrene block copolymer (trade name: Solprene 418)	28.0% by weight
polybutene	5.0% by weight
liquid paraffin	57.0% by weight
rosin ester derivative (trade name: KE-311)	7.5% by weight
3-ℓ-menthoxypropane-1,2-diol	2.0% by weight
suprofen	0.5% by weight

A plaster was obtained in the same manner as in Example 12.

Example 39 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	20.0% by weight
liquid paraffin	40.0% by weight
rosin ester derivative (trade name: KE-311)	34.0% by weight
3-ℓ-menthoxypropane-1,2-diol	4.0% by weight
suprofen	2.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 40 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	20.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	45.0% by weight
rosin ester derivative (trade name: KE-311)	20.0% by weight
3-ℓ-menthoxypropane-1,2-diol	9.0% by weight
estradiol	1.0% by weight

A plaster was obtained in the same manner as in Example 8.

Example 41 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	20.0% by weight
polyisobutylene (trade name: Vistanex)	12.0% by weight
liquid paraffin	37.0% by weight
rosin ester derivative (trade name: Ester Gum H)	20.0% by weight
3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
estradiol	1.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 42 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	22.0% by weight
polyisobutylene (trade name: Vistanex)	6.0% by weight
liquid paraffin	45.0% by weight
rosin ester derivative (trade name: Foral 105)	23.0% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
progesterone	1.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 43 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	15.0% by weight
polyisobutylene (trade name: Vistanex)	10.0% by weight
liquid paraffin	39.0% by weight
rosin ester derivative (trade name: KE-311)	30.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
progesterone	1.0% by weight

A plaster was obtained in the same manner as in Example 11.

Example 44 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	20.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	47.0% by weight
rosin ester derivative (trade name: KE-311)	17.0% by weight
3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
norethisterone	1.0% by weight

A plaster was obtained in the same manner as in Example 12.

Example 45 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1111)	20.0% by weight
polyisobutylene (trade name: Vistanex)	11.0% by weight
liquid paraffin	25.0% by weight
rosin ester derivative (trade name: Ester Gum H)	30.0% by weight
3-ℓ-menthoxypropane-1,2-diol	13.0% by weight
norethisterone	1.0% by weight

A plaster was obtained in the same manner as in Example 10.

Example 46 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1112)	20.0% by weight
polyisobutylene (trade name: Vistanex)	12.0% by weight
liquid paraffin	30.0% by weight
rosin ester derivative (trade name: Foral 105)	30.0% by weight
3-ℓ-menthoxypropane-1,2-diol	7.0% by weight
testosterone	1.0% by weight

A plaster was obtained in the same manner as in Example 9.

Example 47 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	22.0% by weight
polyisobutylene (trade name: Vistanex)	5.0% by weight
liquid paraffin	45.0% by weight
rosin ester derivative (trade name: KE-311)	22.0% by weight
3-*ℓ*-menthoxypropane-1,2-diol	5.0% by weight
testosterone	1.0% by weight

A plaster was obtained in the same manner as in Example 12.

Comparative Example 6 plaster

styrene-isoprene-styrene block copolymer (trade name: Cariflex TR-1107)	20.0% by weight
liquid paraffin	43.5% by weight
polyisobutylene (trade name: Vistanex)	10.0% by weight
rosin ester derivative (trade name: KE-311)	21.5% by weight
diclofenac	1.0% by weight

The components of the above prescription were mixed by a mixer to obtain a paste. The paste was applied on a plastic film previously endowed with releasability, thereon covered with polyester fabric and pressure-contact transferred to obtain a plaster. The prescription of Comparative Example 6 was the same as that of Example 9 except that the former lacked in 3-*ℓ*-menthoxy propane-1,2-diol as a solubilizer.

Example 48 ointment

white vaseline	76.0% by weight
glycerol monostearate	10.0% by weight
beef tallow	10.0% by weight
silicone oil	1.0% by weight
3-*ℓ*-menthoxypropane-1,2-diol	2.0% by weight
flurbiprofen	1.0% by weight

The above components were mixed together under agitation, thereby to prepare an ointment comprising flurbiprofen.

Example 49 ointment

white vaseline	76.95% by weight
diethyl sebacate	5.0% by weight
spermaceti	5.0% by weight
sodium polyoxyethylene-lauryletherphosphate	4.0% by weight
2-hydroxy-4-methoxybenzophenone	1.0% by weight
butyl p-oxybenzoate	0.05% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
ketoprofen	3.0% by weight

The above components were mixed together under agitation, thereby to prepare an ointment comprising ketoprofen.

Example 50 ointment

white vaseline	82.95% by weight
isopropyl myristate	8.0% by weight
spermaceti	3.0% by weight
sodium polyoxyethylene-lauryletherphosphate	2.0% by weight
butyl p-oxybenzoate	0.05% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
indomethacin	1.0% by weight

The above components were mixed together under agitation, thereby to prepare an ointment comprising indomethacin.

Example 51 gel

carboxyvinyl polymer	2.0% by weight
hydroxypropylcellulose	2.0% by weight
ethanol	37.0% by weight
purified water	33.0% by weight
propylene glycol	15.0% by weight
diisopropyladipate	2.0% by weight
diisopropanolamine	2.5% by weight
2-hydroxy-4-methoxybenzophenone	0.5% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by welght
ketoprofen	3.0% by weight

The above components were mixed together under agitation, thereby to prepare a gel comprising ketoprofen.

Example 52 gel

carboxyvinyl polymer	1.5% by weight
hydroxypropylcellulose	2.0% by weight
ethanol	17.0% by weight
purified water	35.3% by weight
propylene glycol	30.0% by weight
propylene carbonate	10.0% by weight
triethanolamine	0.2% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
indomethacin	1.0% by weight

The above components were mixed together under agitation, thereby to prepare a gel comprising indomethacin.

Example 53 gel

carboxyvinyl polymer	1.0% by weight
ethanol	35.0% by weight
purified water	49.0% by weight
propylene glycol	10.0% by weight
diisopropanolamine	1.0% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
flurbiprofen	1.0% by weight

The above components were mixed together under agitation, thereby to prepare a gel comprising flurbiprofen.

Example 54 cream

liquid paraffin	10.0% by weight
middle chain triacylglycerol	5.0% by weight
polyethylene glycol monostearate	3.0% by weight
glycerol	5.0% by weight
carboxyvinyl polymer	1.0% by weight
diisopropanolamine	0.4% by weight
methyl p-oxybenzoate	0.2% by weight
indomethacin	1.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a cream comprising indomethacin.

Example 55 cream

carboxyvinyl polymer	1.0% by weight
isopropyl myristate	5.0% by weight
ethanol	5.0% by weight
polyethylene glycol monostearate	1.0% by weight
coconut oil fatty acid diethanolamide	3.0% by weight
methyl p-oxybenzoate	0.2% by weight
2-hydroxy-4-methoxybenzophenone	0.8% by weight
ketoprofen	3.0% by weight
3-*l*-menthoxypropane-1,2-diol	7.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a cream comprising ketoprofen.

Example 56 cream

carboxyvinyl polymer	1.0% by weight
glycerol	10.0% by weight
ethanol	5.0% by weight
diisopropanolamine	0.4% by weight
middle chain triacylglycerol	3.0% by weight
flurbiprofen	1.0% by weight
3-*l*-menthoxypropane-1,2-diol	5.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a cream comprising flurbiprofen.

Example 57 gel-type cream

carboxyvinyl polymer	1.0% by weight
isopropyl myristate	10.0% by weight
ethanol	5.0% by weight
polyethyleneglycol monostearate	1.0% by weight
methyl p-oxybenzoate	0.2% by weight
coconut oil fatty acid diethanolamide	3.0% by weight
ketoprofen	3.0% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a gel-type cream comprising ketoprofen.

Example 58 gel-type cream

carboxyvinyl polymer	1.0% by weight
isopropyl palmitate	9.0% by weight
diethyl sebacate	9.0% by weight
polyoxyethylene cetylether	2.0% by weight
propylene carbonate	7.0% by weight
methyl p-oxybenzoate	0.2% by weight
sodium hydroxide	0.1% by weight
indomethacin	1.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a gel-type cream comprising indomethacin.

Example 59 gel-type cream

carboxyvinyl polymer	1.5% by weight
cetyl isooctanoate	10.0% by weight
ethanol	5.0% by weight
polyethyleneglycol monostearate	1.0% by weight
methyl p-oxybenzoate	0.2% by weight
coconut oil fatty acid diethanolamide	3.0% by weight
flurbiprofen	3.0% by weight
3-*l*-menthoxypropane-1,2-diol	5.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a gel-type cream comprising flurbiprofen.

Example 60 gel-type cream

carboxyvinyl polymer	1.0% by weight
isopropyl myristate	6.0% by weight
diethyl sebacate	5.0% by weight
polyoxyethylene cethylether	2.0% by weight
propylene carbonate	3.0% by weight
methyl p-oxybenzoate	0.2% by weight
sodium hydroxide	0.1% by weight
ketorolac	3.0% by weight
3-*l*-menthoxypropane-1,2-diol	7.0% by weight
purified water	residual quantity

The above components were mixed together under agitation, thereby to prepare a gel-type cream comprising ketorolac.

Example 61 lotion

ethanol	57.0% by weight
purified water	34.0% by weight
propylene glycol	5.0% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
ketoprofen	1.0% by weight

The above components were mixed together under agitation, thereby to prepare a lotion comprising ketoprofen.

Example 62 lotion

ethanol	38.0% by weight
purified water	50.0% by weight
propylene glycol	6.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
indomethacin	1.0% by weight

The above components were mixed together under agitation, thereby to prepare a lotion comprising indomethacin.

Example 63 lotion

ethanol	30.0% by weight
purified water	50.2% by weight
propylene glycol	10.0% by weight
methylcellulose	0.8% by weight
3-ℓ-menthoxypropane-1,2-diol	7.0% by weight
flurbiprofen	2.0% by weight

The above components were mixed together under agitation, thereby to prepare a lotion comprising flurbiprofen.

Example 64 reserver-type patch

(1)	a backing layer	polyester-type film
(2)	a drug reserving layer	4g of the following gel components were enclosed in the drug reserving layer.
	ketorolac	5.0% by weight
	3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
	carboxyvinyl polymer	2.0% by weight
	propylene glycol	30.0% by weight
	triethyl citrate	19.0% by weight
	purified water	39.4% by weight
	2-hydroxy-4-methoxybenzophenone	0.5% by weight
	diisopropanolamine	1.1% by weight
(3)	a drug releasing layer	Juragard (trade name, a product of Polyplastic Co., Ltd.)
(4)	a pressure-sensitive adhesive layer	silicon-type adhesive

This reserver-type patch consisted of the above (1) - (4) layers and a releasing liner was put on the pressure-sensitive adhesive surface thereby to obtain a laminate.

Example 65 reserver-type patch

(1)	a backing layer	polyester-type film
(2)	a drug reserving layer	4g of the following gel composition were enclosed in the drug reserving layer.
	ketoprofen	3.0% by weight
	3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
	liquid paraffin	70.0% by weight
	stearyl alcohol	20.0% by weight
	d-limonene	2.0% by weight
(3)	a drug releasing layer	Cotran (tradename, a product of 3M Co., Ltd.
(4)	a pressure-sensitive adhesive layer	polyisobutylene-type adhesive

This reserver-type patch consisted of the above (1) - (4) layers and a releasing liner was put on the pressure-sensitive adhesive surface thereby to obtain a laminate.

Example 66 reserver-type patch

(1)	a backing layer	Aluminum laminating polyester film
(2)	a drug reserving layer	4g of the following gel composition were enclosed in the drug reserving layer.
	ketorolac	5.0% by weight
	3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
	silicon	80.0% by weight
	glycerol monolaurate	5.0% by weight
(3)	a drug releasing layer	Cotran
(4)	a pressure-sensitive adhesive layer	silicon-type adhesive (around a support)

This reserver-type patch consisted of the above (1) - (4) layers and a releasing liner was put on the pressure-sensitive adhesive surface thereby to obtain a laminate.

Example 67 reserver-type patch

(1)	a backing layer	Aluminum laminating polyester film
(2)	a drug reserving layer	4g of the following gel composition were enclosed in the drug reserving layer.
	ketorolac	5.0% by weight
	3-ℓ-menthoxypropane-1,2-diol	10.0% by weight
	silicon	80.0% by weight
	glycerol monolauric acid	5.0% by weight
(3)	a drug releasing layer	Cotran
(4)	a pressure-sensitive adhesive layer	silicon-type adhesive (around a support)

This reserver-type patch consisted of the above (1) - (4) layers and a releasing liner was put on the pressure-sensitive adhesive surface to obtain a laminate.

Example 68 reserver-type patch

(1)	a backing layer	Aluminum laminating polyester film
(2)	a drug reserving layer	4g of the following gel composition were enclosed in the drug reserving layer.
	tulobuterol hydrochloride	5.0% by weight
	3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
	stearyl alcohol	10.0% by weight
	cetyl alcohol	10.0% by weight
	behenyl alcohol	10.0% by weight
	propylene glycol	20.0% by weight
	1,3-butylene glycol	35.0% by weight
	lauryl alcohol	5.0% by weight
(3)	a drug releasing layer	Cotran
(4)	a pressure-sensitive adhesive layer	silicon-type adhesive (around a support)

This reserver-type patch consisted of the above (1) - (4) layers and a releasing liner was put on the pressure-sensitive adhesive surface to obtain a laminate.

Example 69 liniment

ethanol	45.0% by weight
2-hydroxy-4-methoxybenzophenone	0.6% by weight
diisopropyl adipate	30.0% by weight
α-tocopherol	1.0% by weight
hydroxypropylcellulose	1.5% by weight
ketoprofen	2.0% by weight
3-ℓ-menthoxypropane-1,2-diol	4.0% by weight
purified water	15.9% by weight

The above components were mixed together under agitation, thereby to prepare a lotion comprising ketoprofen.

Example 70 liniment

propyleneglycol	10.0% by weight
2-hydroxy-4-methoxybenzophenone	0.2% by weight
polypropyleneglycol monolaurate	10.0% by weight
crotamiton	0.5% by weight
acetone	18.0% by weight
ethyl alcohol	20.0% by weight
ethanol	28.8% by weight
ketoprofen	0.5% by weight
3-ℓ-menthoxypropane-1,2-diol	2.0% by weight
purified water	10.0% by weight

The above components were mixed together under agitation, thereby to prepare a liniment comprising ketoprofen.

Example 71 liniment

polyethyleneglycol 400	45.0% by weight
2-hydroxy-4-methoxybenzophenone	0.5% by weight
α-tocopherol	1.0% by weight
isopropylalcohol	31.5% by weight
ethanol	40.0% by weight
ketorolac	5.0% by weight
3-ℓ-menthoxypropane-1,2-diol	7.0% by weight
purified water	7.0% by weight

The above components were mixed together under agitation, thereby to prepare a liniment comprising ketorolac.

Example 72 liniment

polypropyleneglycol monolaurate	15.0% by weight
2,2-hydroxy-4-methoxybenzophenone	0.7% by weight
diisopropyl adipate	4.0% by weight
α-tocopherol	1.0% by weight
denatured alcohol of 3-acetylsucrose	49.6% by weight
ketorolac	3.0% by weight
3-ℓ-menthoxypropane-1,2-diol	5.0% by weight
purified water	21.7% by weight

The above components were mixed together under agitation, thereby to prepare a liniment comprising ketorolac.

Example 73 aerosol

4.5% by weight of camphor, 4.0% by weight of 3-ℓ-menthoxypropane-1,2-diol, 3.0% by weight of ketoprofen and 1.0% by weight of 2-hydroxy-4-methoxybenzophenone were solubilized in 32.5% by weight of ethanol, incorporated with 26.0% by weight of water, charged into an aerosol container and then incorporated with 4.0% by weight of talc to prepare a pharmaceutical solution, after which a mixed propellant composed of 13.0% by weight of dimethyl ether and 12.0% by weight of liquefied petroleum gas was injected into the container, thereby to obtain an anti-inflammatory and analgetic aerosol. The above weight percentages were respectively based on the whole quantity.

Example 74 aerosol

4.5% by weight of camphor, 0.4% by weight of diphenhydramine, 5.0% by weight of 3-ℓ-menthoxypropane-1,2-diol, 1.0% by weight of ketorolac and 1.0% by weight of α-tocopherol were solubilized in 30.1% by weight of ethanol, incorporated with 24.0% by weight of water to the obtained solution, and then charged into an aerosol container, after which a mixed propellant composed of 25.0% by weight of dimethyl ether and 9.0% by weight of liquefied petroleum gas was injected into the container, thereby to obtain an anti-inflammatory and analgetic aerosol, wherein the ratios were respectively based on the whole quantity.

Example 75 creamy-type pack

liquid paraffin	10.0% by weight
cetanol	1.0% by weight
sorbitan monostearate	3.0% by weight
POE (20) sorbitan monostearate	3.0% by weight
1,3-butylene glycol	5.0% by weight
glycerol	3.0% by weight
methyl paraben	0.2% by weight
stearyl glycylrhetinate	0.1% by weight
3-ℓ-menthoxypropane-1,2-diol	1.0% by weight
purified water	73.7% by weight

The above components were mixed together under agitation, thereby to prepare a cream-type pack.

Example 76 clay-type pack

kaolin	20.0% by weight
talc	8.0% by weight
glycerol	3.0% by weight
propylene glycol	3.0% by weight
carboxymethyl cellulose	0.3% by weight
POE (20) sorbitan monooleate	2.0% by weight
methyl paraben	0.1% by weight
L-ascorbyl stearate	0.2% by weight
3-ℓ-menthoxypropane-1,2-diol	3.0% by weight
purified water	60.4% by weight

The above components were mixed together under agitation, thereby to prepare a clay-type pack.

Example 77 foam-type pack

stearic acid	5.0% by weight
behenic acid	5.0% by weight
cetanol	1.0% by weight
squalane	4.0% by weight
glycerol	15.0% by weight
POE (40) monostearate	1.0% by weight
ethyl paraben	0.1% by weight
L-ascorbyl palmitate	0.05% by weight
3-ℓ-menthoxypropane-1,2-diol	0.5% by weight
purified water	68.35% by weight

The above components were mixed together under agitation, thereby to prepare a liquid. Thereafter the liquid was injected with a liquefied petroleum gas into a container to obtain a foam-type pack.

Example 78 pressure-sensitive adhesive-type sheet pack

gelatin	8.0% by weight
glycerol	25.0% by weight
sorbitol	7.0% by weight
sodium polyacrylate	2.0% by weight
polyvinyl alcohol	2.0% by weight
aluminium hydroxide	1.0% by weight
methyl paraben	0.05% by weight
isopropyl methylphenol	0.01% by weight
3-ℓ-menthoxypropane-1,2-diol	0.005% by weight
purified water	54.935% by weight

The above components were mixed together under agitation, thereby to obtain a paste. The paste was spread on a nonwoven fabric, covered thereon with a release film to obtain a laminate. The laminate was cut into pieces each having a predetermined form to obtain adhesive-type sheet packs.

Example 79 impregnation-type sheet pack

glycerol	10.0% by weight
1,3-butylene glycol	10.0% by weight
sodium hyaluroniate	0.1% by weight
methyl paraben	0.1% by weight
glycyrrhizinic acid	0.01% by weight
3-ℓ-menthoxypropane-1,2-diol	0.05% by weight
purified water	79.74% by weight

The above components were mixed together under agitation, thereby to obtain a mixture. The mixture was impregnated into a nonwoven fabric, covered thereon with a release film to obtain a laminate. The laminate was cut into pieces each having a predetermined form to obtain impregnation-type sheet packs.

Example 80 peel-off pack

polyvinyl alcohol	20.0% by weight
carboxymethyl cellulose	3.0% by weight
titanium oxide	8.0% by weight
1,3-butylene glycol	5.0% by weight
squalane	3.0% by weight
POE (10) nonylphenyl ether	0.5% by weight
methyl paraben	0.1% by weight
calciferol	0.01% by weight
3-ℓ-menthoxypropane-1,2-diol	0.1% by weight
purified water	60.29% by weight

The above components were mixed together under agitation, thereby to obtain peel-off packs.

Comparative Example 7 cream-type pack

The procedure of Example 73 was followed except that the 3-ℓ-menthoxypropane-1,2-diol was not used, thereby to obtain a cream-type pack.

Comparative Example 8 adhesive-type sheet pack

The procedure of Example 78 was followed except that the 3-ℓ-menthoxypropane-1,2-diol was not used, thereby to obtain a adhesive-type sheet pack.

Test Example 1

The plasters of Example 7 and Comparative Examples 4 and 5 were stored at 5°C for two weeks, while they were observed with the lapse of time to find whether the drug crystallized or not. The results are given in Table 1.

Table 1

Sample	initial	1 day	3 days	7 days	14 days
plaster of Ex. 7	o	o	o	o	o
plaster of Comp. Ex. 4	x	x	x	x	x
plaster of Comp. Ex. 5	o	x	x	x	x
o: no crystallization was found x: crystallization was found					

As apparent from the above results, the plaster of Example 7 containing 3-ℓ-menthoxypropane-1,2-diol as the solubilizer contained clonidine in its solubilized state in the base even after the lapse of two weeks, while the plaster of Comparative Example 4 containing no solubilizer and that of Comparative Example 5 containing isopropyl myristate suffered from the crystallization of clonidine in their respective bases. Thus, the above results supported the usefulness of 3-ℓ-menthoxypropane-1,2-diol as the solubilizer for clonidine.

Test Example 2 (adhesion test)

The poultices of Examples 1 to 4 and Comparative Examples 1 to 3 were examined for their adhesion and changes thereof time according to the Nichiban Rolling Ball method. This method is such that a ball is so rolled along a poultice sample from a predetermined height at an angle of 30°C as to draw a sine curve, to measure a distance from a point where the rolling ball reaches the smple to a point where it stops rolling. Accordingly, a shorter distance of roll or a bigger ball means a more excellent adhesion. In this test, a poultice sample having a length of 140 mm was spread with its adhesive side up and a stainless steel ball (20/32 inch, JIS) was rolled along the sample to determine the distance of roll of the ball. The results are given in Table 2.

Table 2

Pressure-sensitive Adhesive tape	Initial adhesion (mm)	After storage for 6 months at 40°C(mm)
Ex. 1	50	48
Ex. 2	30	33
Ex. 3	35	38
Ex. 4	43	41
Comp. Ex. 1	98	95
Comp. Ex. 2	78	82
Comp. Ex. 3	passed through	passed through

As apparent from the above results, the polutices of Examples 1 to 4 exhibited excellent adhesion and the adhesion did not change even after the lapse of time.

Test Example 3 (test on safety for the skin)

The poultices of Examples 1 to 4 and Comparative Examples 1 to 3 were examined for safety for the skin.

The safety of each poultice for the skin was determined by 25 healthy male and female subjects according to the 48-hour closed patch test. The change in the skin of each subject was determined by observation 1 and 24 hours after the peeling of the patch, and the irritativeness of the poultice was evaluated according to the following criteria. The results are given in Tables 3 and 4.

-: no change in the skin
±: slight rubefaction
+: clear rubefaction
++: heavy contact dermatitis

Table 3

Time which has elapsed after peeling	Judgement Sample	++	+	±	-	Total (subjects)	Rate (%) of positive reaction (±,+ and ++)
1 hr	Ex. 1	0	0	0	25	25	0.0
1 hr	Ex. 2	0	0	1	24	25	4.0
1 hr	Ex. 3	0	0	0	25	25	0.0
1 hr	Ex. 4	0	0	0	25	25	0.0
1 hr	Comp.Ex.1	0	0	2	23	25	8.0
1 hr	Comp Ex.2	0	0	1	24	25	4.0
1 hr	Comp Ex.3	0	0	3	22	25	12.0

Table 4

Time which has elapsed after peeling	Judgement Sample	++	+	±	-	Total (subjects)	Rate (%) of positive reaction (±,+ and ++)
24 hrs	Ex. 1	0	0	0	25	25	0.0
24 hrs	Ex. 2	0	0	0	25	25	0.0
24 hrs	Ex. 3	0	0	0	25	25	0.0
24 hrs	Ex. 4	0	0	0	25	25	0.0
24 hrs	Comp.Ex.1	0	0	1	24	25	4.0
24 hrs	Comp Ex.2	0	0	0	25	25	0.0
24 hrs	Comp Ex.3	0	0	1	24	25	4.0

As apparent from the above results, the poultices of Examples 1 to 4 exhibited extremely high safety for the skin.

Test Example 4 (test on human percutaneous absorption)

The poultices of Example 4 and Comparative Example 2 were each die-cut into samples (3 × 3 cm^2). These samples were applied to the upper backs of eight healthy subjects respectively. After 8 hours, the samples were peeled and examined for the amount of ketoprofen remaining in the peeled samples by HPLC (high performance liquid chromatography). The calculation of human absorption rate, the determination of amount of the remaining ketoprofen and HPLC were conducted as follows:

(1) human absorption rate = (1 - remaining amount/initial content) × 100
(2) determination of amount of residue of ketoprofen
Each peeled sample was extracted with 70 ml of methanol under reflux and the extract was diluted with methanol to 100 ml. The resulting dilution was used as the sample for HPLC.
(3) Conditions of HPLC
mobile phase; 0.2% aqueous solution of acetic acid : acetonitrile = 55 : 45
detection wavelength; 254 nm
column; TSK gel ODS-80TM
flow rate; 1.0 μℓ/min.

Table 5

	Human absorption rate (%)
Ex. 4	12.7
Comp. Ex. 2	5.0

As shown in Table 5, the poultice of Example 4 containing 3-ℓ-menthoxypropane-1,2-diol as the solubilizer exhibited a higher absorption rate than that of the poultice of Comparative Example 2.

Test Example 5

The plasters of Example 9 and Comparative Example 6 were stored at 5°C, while they were observed with the lapse of time to determine whether crystallization occurred or not. The results are given in Table 6.

Table 6

Sample	initial	1 day	3 days	7 days	14 days
Ex. 9	o	o	o	o	o
Comp. Ex. 6	o	o	x	x	x
o: no crystallization was found x: crystallization was found					

As apparent from the results given in Table 6, the plaster of Example 9 contained diclofenac in a solubilized state in the base even after the lapse of time, though that of Comparative Example 6 containing no solubilizer suffered from the crystallization of diclofenac. Thus, the above results supported the usefulness of 3-ℓ-menthoxypropane-1,2-diol as the solubilizer for diclofenac.

Test Example 6 (test on human pecutaneous absorption)

The plasters of Example 9 and Comparative Example 6 were each die-cut into samples (3 × 3 cm^2). These samples were applied to the upper backs of six healthy subjects respectively. After 8 hours, the samples were peeled and examined for the residual amount of diclofenac by HPLC. The calculation of human absorption rate, the determination of residual amount of diclofenac and HPLC were conducted as follows:

(1) human absorption rate = (1 - residual amount/initial content) × 100

(2) determination of residual amount of diclofenac:

Each peeled sample was subjected to ultrasonic extraction with 30 ml of tetrahydrofuran for 2 hours and the extract was diluted with tetrahydrofuren to 50 ml. The resulting dilution was used as the sample for HPLC.

(3) Conditions of HPLC

mobile phase; 0.2% aqueous solution of acetic acid : acetonitrile = 1 : 1
detection wavelength; 275 nm
column; TSK gel ODS-80TM
flow rate; 1.0 μℓ/min.

The results are given in Fig. 1. As apparent from Fig. 1, the plaster of Example 9 exhibited a significantly enhanced absorption rate as compared with that of Comparative Example 6. In other words, the plaster of Example 9 could contain diclofenac in a solubilized state by virtue of the solubilizability of 3-ℓ-menthoxypropane-1,2-diol thereby to give excellent release of diclofenac.

Test Example 7

The packs of Examples 75 and 78 and Comparative Examples 7 and 8 were stored at 5°C for two weeks, while they were observed with the lapse of time to determine whether the fat-soluble powder crystallized or not. The results are

given in Table 7.

Table 7

	initial	1 day	3 days	7 days	14 days
Ex. 75	o	o	o	o	o
Ex. 78	o	o	o	o	o
Comp. Ex. 7	x	x	x	x	x
Comp. Ex. 8	o	x	x	x	x
o: no crystallization was found x: crystallization was found					

The above results supported the usefulness of 3-ℓ-menthoxypropane-1,2-diol as the solubilizer for a fat-soluble powder.

Test Example 8

The packs of Example 75 and Comparative Example 7 were examined organoleptically by ten female subjects. The results are given in Table 8.

Table 8

		Ex. 75	Comp. Ex. 7
Odor	observed	0	0
	not observed	10	10
Refreshing effect	observed	10	0
	not observed	0	10
Irritation to the skin	observed	0	0
	not observed	10	10
Stickiness	observed	0	1
	not observed	10	9
Roughness	observed	1	8
	not observed	9	2

It can be understood from the above results that the pack of Example 75 has refreshing or refrigerant effect and is freed from the crystallization of a fat-soluble powder thereby to be excellent in feelings in use.

Industrial Applicability

According to the present invention, 3-ℓ-menthoxypropane-1,2-diol which has been used as a refrigerant is used as a solubilizer for a pharmaceutically effective ingredient and this compound exhibits high solubilizability for a pharmaceutically effective ingredient and is excellent in safety, stability and compatibility. Accordingly, a percutaneously absorbable preparation (which is one of external preparations) containing said compound is improved in the release of a pharmaceutically effective ingredient from the base and the pecutaneous absorption of the effective agent. Further, such a preparation causes little side effects such as contact dermatitis even when applied repeatedly and is not irritant to the skin thereby to be extremely safe. Furthermore, the preparation is odorless and can impart comfortable refreshing refrigeration to the skin.

Accordingly, the external preparation of the present invention is suited for percutaneously absorbable preparations and packs, thus having high industrial applicability.

Claims

1. A solubilizer for a pharmaceutically effective ingredient, which comprises 3-ℓ-menthoxypropane-1,2-diol.

2. An external preparation comprising a pharmaceutically effective ingredient and a solubilizer therefor which comprises 3-ℓ-menthoxypropane-1,2-diol.

3. An external preparation as set forth in claim 2, wherein the content of said 3-ℓ-menthoxypropane-1,2-diol is 0.001 to 20% by weight.

4. An external preparation as set forth in claim 2, which is a percutaneously absorbable preparation containing a drug as said pharmaceutically effective ingredient.

5. An external preparation as set forth in claim 4, wherein said content of 3-ℓ-menthoxypropane-1,2-diol is 0.1 to 20% by weight.

6. An external preparation as set forth in claims 4 or 5, which has a dosage form selected from the group consisting of poultice, plaster, ointment, gel, cream, gel-type cream, lotion, reserver-type patch, liniment and aerosol.

7. An external preparation as set forth in claim 6, which is a poultice whose base comprises at least one member selected from a water-soluble polymer, a higher alcohol and water in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

8. An external preparation as set forth in claim 6, which is a plaster whose base comprises at least one member selected from a rosin ester derivative as a solubilizer for the drug, a styrene-isoprene-styrene block copolymer, an acrylic adhesive, and a softening agent in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

9. An external preparation as set forth in claim 6, which is an ointment whose base comprises at least one member selected from a higher fatty acid and an ester thereof, a wax, a surfactant and a hydrocarbon in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

10. An external preparation as set forth in claim 6, which is a gel whose base comprises at least one member selected from a lower alcohol, water, a gelling agent and a neutralizing agent in addition to said 3-ℓ-methoxypropane-1,2-diol and drug.

11. An external preparation as set forth in claim 6, which is a cream whose base comprises at least one member selected from a higher fatty acid ester, water, a hydrocarbon and an emulsifying agent in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

12. An external preparation as set forth in claim 6, which is a gel-type cream whose base comprises at least one member selected from a higher fatty acid ester, a lower alcohol, an emulsifying agent, a neutralizing agent and a gelling agent in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

13. An external preparation as set forth in claim 6, which is a lotion whose base comprises at least one member selected from a lower alcohol, water and/or a glycol in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

14. An external preparation as set forth in claim 6, which is a reserver-type patch wherein the base of the drug reserving layer comprises any one selected from the group consisting of

    (a) a mixture comprising at least one member selected from a glycol, a lower alcohol, water and a water-soluble polymer,
    (b) a mixture comprising at least one member selected from an aliphatic alcohol and a polyhydric alcohol and
    (c) a mixture comprising at least one member selected from a paraffin and a silicon compound, in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

15. An external preparation as set forth in claim 6, which is a liniment whose base comprises at least one member selected from an alcohol, water and a fatty acid ester in addition to said 3-ℓ-menthoxypropane-1,2-diol and drug.

16. An external preparation as set forth in claim 6, which is an aerosol whose base comprises at least one member selected from a lower alcohol, water, dimethyl ether and/or liquefied petroleum gas in addition to said 3-*ℓ*-menthoxypropane-1,2-diol and drug.

17. An external preparation as set forth in claim 2 or 3, which is a pack containing a fat-soluble powder as the pharmaceutically effective ingredient.

18. An external preparation as set forth in claim 17, wherein the content of said 3-*ℓ*-menthoxypropane-1,2-diol is 0.001 to 5% by weight.

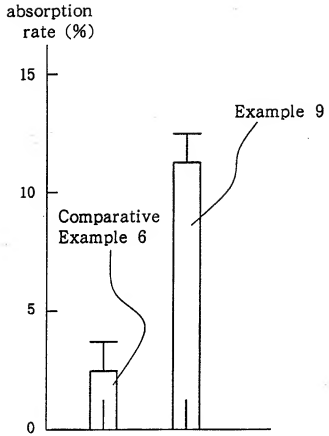

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP94/00800

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl[5] A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl[5] A61K47/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 57-98209 (Kohwa Corp.), June 18, 1982 (18. 06. 82), Lines 12 to 16, column 1, (Family: none)	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
June 6, 1994 (06. 06. 94)	June 28, 1994 (28. 06. 94)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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